Long-term risk of subsequent tumors in childhood cancer survivors

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2018

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CHAPTER 4

Colorectal adenomas and cancers after childhood cancer treatment: a DCOG-LATER record linkage study

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Journal of the National Cancer Institute 2018; 110(7): djx266

ABSTRACT

Background

Although colorectal adenomas serve as prime target for colorectal cancer (CRC) surveillance in other high-risk groups, data on adenoma risk after childhood cancer is lacking. We evaluated the risk of histologically confirmed colorectal adenomas among childhood cancer survivors. A secondary aim was to assess CRC risk.

Methods:

The DCOG-LATER cohort study includes five-year Dutch childhood cancer survivors and a sibling comparison group (n = 883). Colorectal tumors were identified from the population-based Dutch Pathology Registry (PALGA). We calculated cumulative incidences of adenomas/CRCs for survivors and siblings. For adenomas, multivariable Cox regression models were used to evaluate potential risk factors. All statistical tests were two-sided.

Results

Among 5843 five-year survivors (median follow-up = 24.9 years), 78 individuals developed an adenoma. Cumulative incidence by age 45 was 3.6% (95% confidence interval [CI] = 2.2% to 5.6%) after abdominopelvic radiotherapy (AP-RT; 49 cases) vs. 2.0% (95% CI = 1.3% to 2.8%) among survivors without AP-RT (28 cases; $P_{difference}$=.07), and vs. 1.0% (95% CI = 0.3% to 2.6%) among siblings (6 cases) ($P_{difference}$=.03). Factors associated with adenoma risk were AP-RT (hazard ratio [HR] = 2.12; 95% CI = 1.24 to 3.60), total body irradiation (TBI; HR = 10.55, 95% CI = 5.20 to 21.42), cisplatin (HR = 2.13; 95% CI = 0.74 to 6.07 for <480 mg/m²; HR = 3.85, 95% CI = 1.45 to 10.26 for ≥480 mg/m²; P_{trend}=.62), a hepatoblastoma diagnosis (HR = 27.12, 95% CI = 8.80 to 83.58), and family history of early-onset CRC (HR=20.46, 95% CI = 8.10 to 51.70). Procarbazine was statistically significantly associated among survivors without AP-RT/TBI (HR=2.71; 95% CI = 1.28 to 5.74). Thirteen CRCs occurred.

Conclusion

We provide evidence for excess risk of colorectal adenomas and CRCs among childhood cancer survivors. Adenoma risk factors include AP-RT, TBI, cisplatin, and procarbazine. Hepatoblastoma (familial adenomatous polyposis-associated) and family history of early-onset CRC were confirmed as strong risk factors. A full benefit-vs-harm evaluation of CRC screening among high-risk childhood cancer survivors warrants consideration.

INTRODUCTION

In recent years, evidence has mounted for an elevated incidence of colorectal cancer (CRC) among (young) adults who received high-dose abdominal radiotherapy decades earlier and, perhaps, also among those who received alkylating agent-based chemotherapy.[1-4] These findings have spurred debate on the need for early detection programs among childhood cancer survivors[1-4] to find CRC precursors, that is, adenoma or early-stage CRC amenable to curative treatment.[5-7] A recent study of early colonoscopic screening (age 35—49) among 54 childhood cancer survivors treated with high-dose abdominal radiotherapy revealed an adenomatous polyp prevalence comparable with that among the average-risk population age 50 years or older.[8] To our knowledge, there have been no published data on the risk of and treatment-related risk factors for colorectal adenomas among childhood cancer survivors not involved in colorectal tumor surveillance programs.

In the general population and among individuals with cancer susceptibility syndromes, most CRCs are preceded by adenomas.[9,10] Timely removal of adenomas reduces CRC incidence and mortality,[11,12] providing the rationale for CRC screening in these settings.[5-7]

We aimed to determine the risk of histologically confirmed colorectal adenomas and cancers in a large cohort of five-year childhood cancer survivors not subject to systematic colorectal tumor screening and a sibling comparison group. Moreover, we quantified contributions of abdominopelvic radiotherapy, specific chemotherapeutic agents, and indicators of colorectal tumor predisposition in the etiology of adenomas.

METHODS

Study cohort

The DCOG-LATER cohort includes five-year survivors of childhood cancer originally diagnosed between January 1, 1963, and December 31, 2001, younger than age 18 years in one of seven Dutch pediatric oncology and stem cell transplant centers, as reported previously.[13] The study protocol was declared exempt from review of medical intervention research by institutional review boards of all participating centers.

Information on cancer diagnosis, treatment and family history of colorectal cancer

Details on prior cancer diagnosis and treatment for primary tumor and any recurrences were collected from original medical files.[13] Here, we further specified abdominopelvic radiation exposure by estimating the colorectal tract volume directly exposed to radiation. A pediatric radiation oncologist (WD) and a radiation technologist (JK) determined the estimated proportion of total colorectal volume exposed based on the childhood cancer-

specific coded treatment fields. Also, anatomy/position information of the colorectum was used, based on specific experience, anatomy text books, and a sample of available radiotherapy simulation films from fields involving the abdomen (Supplementary Table 1). Discrepancies were discussed (JCT) until consensus was achieved. Total body irradiation (TBI) was evaluated separately. Information on family history of early-onset CRC (CRC before age 50 years in first-degree relatives) was collected in the 2013—2014 DCOG-LATER questionnaire survey and from medical records.

Vital status and colorectal tumor outcome ascertainment

Vital status and emigration status for all survivors were obtained from the Municipal Person Records Database, linkage to the Central Office of Genealogy, or from the last known municipality of residence.[13] Colorectal tumors were identified by linkage with the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), which was established in 1970 and which attained full nationwide coverage in 1990.[14] Linkage was based on family name, sex, and birth date. We included all pathology excerpts with PALGA codes for colorectal adenomas and cancers (detailed in Supplementary Table 2) in the period January 1, 1990, to January 9, 2017. For all adenomas we sought medical file review in the DCOG-LATER academic centers to retrieve the indication for colonoscopy, coded as follows: 1) specific colorectal tumor-related symptoms; 2) screening or surveillance colonoscopy because of a (possible) genetic predisposition for developing colorectal tumors; 3) screening or surveillance colonoscopy for other reasons; 4) accidental finding on imaging/colonoscopy for reasons other than a suspected colorectal tumor.

Eligible study population survivors and siblings

From the DCOG-LATER cohort (6165 five-year survivors), we excluded individuals who opposed use of health care data (n = 152), and those who died, emigrated, or were lost to follow-up prior to 1990 (n = 170) (Supplementary Figure 1). Survivors who participated in the 2013—2014 questionnaire survey (n = 3172) were asked to invite their respective siblings. In total, 883 of 1663 (53%) approached siblings were eligible for this study, and colorectal adenomas and cancers were ascertained as described above.

Statistical analyses

Time at risk started five years after childhood cancer diagnosis or January 1, 1990 (date full nationwide coverage PALGA), whichever came last, and ended at the date of diagnosis of the first adenoma, date of death, date of emigration, date of loss to follow-up, or end of study (January 9, 2017), whichever came first. To describe heterogeneity in the cohort, the distribution of person-years and the crude adenoma rate/10 000 person-years were graphically depicted by childhood cancer type, stratified by age or by radiotherapy

to the colorectal area (abdominopelvic radiotherapy/TBI). Cumulative incidence of histologically confirmed adenomas was estimated, treating death as a competing risk. Cumulative incidences were compared between (subgroups of) survivors and siblings with pairwise Pepe-Mori tests.[15] Multivariable Cox proportional hazards models were used to examine the effect of potential risk factors on subsequent adenoma risk (as detailed in the Supplementary Methods and Supplementary Table 3). We chose attained age as the time scale to take into account expected variation in colon adenoma risk with increasing age.[16] Although the main focus was on treatment factors, we added indicator variables for hepatoblastoma and medulloblastoma to the final model to ascertain the anticipated influence of genetic susceptibility to colorectal tumors, because these childhood tumors cluster among individuals affected by familial adenomatous polyposis (FAP).[17] We evaluated the proportional hazards assumption by visual inspection of log-minus-log survival curves and Schoenfeld residuals vs attained age. We calculated standardized incidence ratios (SIRs) and excess absolute risks per 10 000 person-years of follow-up (EARs) for CRC. Expected numbers were based on age-, sex-, and calendar year-specific rates from the Netherlands Cancer Registry.[13-18] All analyses were performed using Stata, version 13 (Stata Statistical Software, Release 13, StataCorp., College Station, TX). All statistical tests were two-sided. For all analyses, a P value of less than .05 was considered statistically significant.

RESULTS

Cohort characteristics

This analysis included 5843 five-year survivors (97.4% with complete follow-up during 1990—2017) who contributed 112 157 person-years at risk. The median time since childhood cancer diagnosis was 24.9 years (range = 5.0—3.9 years), and the median attained age at end of follow-up was 32.4 years (range = 5.8-69.2 years) for survivors and 32.2 years (range = 11.4-73.3 years) for siblings. In total, 78 (1.3%) survivors developed at least one adenoma compared with 6 of 883 (0.7%) siblings (Table 1). Survivors with adenoma had a higher attained age at end of follow-up than the cohort as a whole. More than half of the survivors with an adenoma developed multiple adenomas, and six patients (7.7%) developed more than 10 adenomas. Compared with the eligible cohort, patients with adenoma were seemingly more often diagnosed with childhood cancer prior to 1980 and were more likely to have received radiotherapy to the colorectal area, procarbazine, and cisplatin (Table 2).

TABLE 1. Characteristics of the total DCOG-LATER cohort of survivors eligible for analyses (n = 5,843), of survivors who developed a colorectal adenoma (n = 78), of the total sibling comparison group (n = 883), and of siblings who developed a colorectal adenoma (n = 6)

	Childhood cancer survivors				Siblings			
	Total survivor cohort		Colorectal adenoma patients		Total sibling cohort		Colorectal adenoma patients	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	3,269	56.0	43	55.1	363	41.1	4	66.7
Female	2,574	44.1	35	44.9	520	58.9	2	33.3
Attained age, y								
<30	2,386	40.8	17	21.8	370	41.9	2	33.3
30-39	2,014	34.5	27	34.6	285	32.3	2	33.3
40+	1,443	24.7	34	43.6	228	25.8	2	33.3
Pathological subtype of first adenoma								
Tubular adenoma	NA	NA	44	56.4	NA	NA	2	33.3
Tubulovillous adenoma	NA	NA	16	20.5	NA	NA	0	0.0
Adenoma, NOS	NA	NA	9	11.5	NA	NA	4	66.6
Synchronous multiple subtypes*	NA	NA	9	11.5	NA	NA	0	0.0
Localization of first adenoma								
Colon	NA	NA	55	70.5	NA	NA	6	100.0
Rectum	NA	NA	10	12.8	NA	NA	0	0.0
Synchronous diagnosis in both colon vand rectum	NA	NA	9	11.5	NA	NA	0	0.0
Unknown	NA	NA	4	5.1	NA	NA	0	0.0
Number of adenomas								
1	NA	NA	37	47.4	NA	NA	4	66.7
2-5	NA	NA	28	35.9	NA	NA	1	16.7
6-10	NA	NA	4	5.1	NA	NA	0	0.0
10+	NA	NA	6	7.7	NA	NA	0	0.0
Multiple, exact number unknown	NA	NA	3	3.9	NA	NA	1	16.7
Calendar period of first colorectal adenoma diagnosis								
1990-1999	NA	NA	2	2.6	NA	NA	0	0.0
2000-2009	NA	NA	16	20.5	NA	NA	2	33.3
2010-2017	NA	NA	60	76.9	NA	NA	4	66.6

Abbreviations: NA, not applicable; NOS, not otherwise specified.
Numbers do not always add up to 100% because of missing values or rounding.
* Includes patients with a synchronous adenoma diagnosis of tubular adenoma and tubulovilllous adenoma (n = 5), tubular adenoma and serrated adenoma (n = 2), tubulovillous adenoma and villous adenoma (n = 1), and tubular adenoma, tubulovillous adenoma, and serrated adenoma (n = 1).

TABLE 2. Childhood cancer diagnosis and treatment characteristics of the total DCOG-LATER cohort of survivors eligible for analyses (n = 5,843) and of survivors who developed a colorectal adenoma (n = 78)

	Total survivor cohort		Colorectal adenoma patients	
Childhood cancer survivors	**No.**	**%**	**No.**	**%**
Childhood cancer type				
Acute lymphoblastic leukemia	1,696	29.0	12	15.4
Acute myeloid leukemia	187	3.2	5	6.4
Non-Hodgkin lymphoma	555	9.5	5	6.4
Hodgkin lymphoma	395	6.8	11	14.1
Medulloblastoma	153	2.6	2	2.6
Other central nervous system tumors	628	10.8	7	9.0
Renal tumors	578	9.9	6	7.7
Hepatoblastoma	43	0.7	4	5.1
Sarcoma	769	13.2	16	20.5
Other tumors	839	14.4	10	12.8
Age at childhood cancer diagnosis, y				
<5	2,641	45.2	23	29.5
5-9	1,583	27.1	21	26.9
10+	1,619	27.7	34	43.6
Time since childhood cancer diagnosis, y				
<20	1,697	29.0	17	21.8
20-39	3,692	63.2	47	60.3
40+	454	7.8	14	18.0
Calendar year of childhood cancer diagnosis				
1963-1979	924	15.8	34	43.6
1980-1989	1,851	31.7	23	29.5
1990-2001	3,068	52.5	21	26.9
Vital status				
Dead	484	8.3	8	10.3
Alive	5,359	91.7	70	89.7
Radiotherapy*				
No	3,505	60.0	30	38.4
Yes	2,308	39.5	47	60.3
Radiotherapy to the colorectal area*				
Abdominopelvic radiotherapy no - TBI no	4,796	82.1	49	62.8
Abdominopelvic radiotherapy yes - TBI no	794	13.6	18	23.1
Abdominopelvic radiotherapy no - TBI yes	203	3.5	8	10.3
Abdominopelvic radiotherapy yes - TBI yes	7	0.1	2	2.6

TABLE 2 (CONTINUED).

	Total survivor cohort		Colorectal adenoma patients	
Childhood cancer survivors	**No.**	**%**	**No.**	**%**
Chemotherapy*				
No	1,050	18.0	15	19.2
Yes	4,759	81.5	61	78.2
Alkylating agents*				
No	2,820	48.3	35	44.9
Yes	2,987	51.1	41	52.6
Procarbazine*				
No	5,397	92.4	66	84.6
Yes	407	7.0	10	12.8
Anthracyclines*				
No	3,117	53.4	46	59.0
Yes	2,690	46.0	30	38.5
Epipodophyllotoxins*				
No	4,573	78.3	60	76.9
Yes	1,232	21.1	16	20.5
Vinca alkaloids*				
No	1,599	27.4	27	34.6
Yes	4,210	72.1	49	62.8
Platinum agents*				
No	5,035	86.2	66	84.6
Yes	770	13.2	10	12.8
Cisplatin*				
No	5,371	91.9	67	85.9
Yes	433	7.4	9	11.5
Carboplatin*				
No	5,396	92.4	74	94.9
Yes	409	7.0	2	2.6
Antimetabolites*				
No	3,087	52.8	48	61.5
Yes	2,721	46.6	28	35.9
Hematopoietic cell transplantation*				
No	5,404	92.5	65	83.3
Yes	371	6.4	11	14.1
Family history of early-onset CRC†				
No/unknown	5,849	99.5	73	93.6
Yes	15	0.3	5	6.4

Abbreviations: NA, not applicable; TBI, total body irradiation.

Numbers do not always add up to 100% because of missing values or rounding.

* Treatment data include primary treatment and all recurrences; radiotherapy (yes/no), radiotherapy to the colorectal area (yes/no), chemotherapy (yes/no), and hematopoietic cell transplantation (yes/no) were missing for 30, 41, 34, and 68 survivors, respectively.

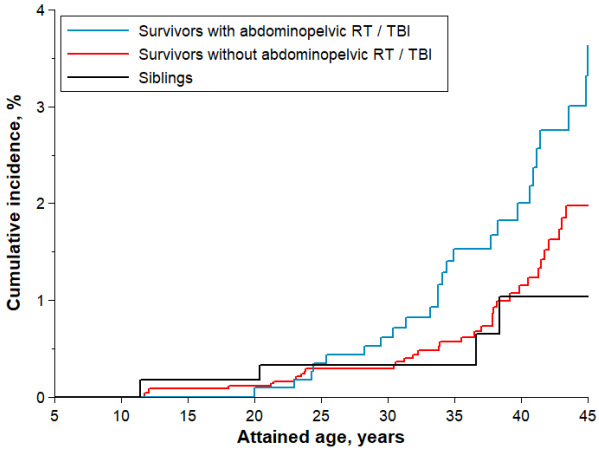
† Defined as having a first-degree relative affected by colorectal cancer before age 50 years.

Cohort distribution of age and abdominopelvic radiotherapy/TBI

The adenoma rate appeared to be highest among individuals age 40 years or older (red bars in Supplementary Figure 2A). In all, survivors of renal tumors seemed to be the most likely to have received abdominopelvic radiotherapy/TBI (40.4%, gray bars in Supplementary Figure 2B). Moreover, survivors with abdominopelvic radiotherapy/TBI appeared to have higher adenoma rates than survivors without such treatments, in particular following leukemia, renal tumors, and sarcoma (red bars in Supplementary Figure 2B).

Cumulative incidence colorectal adenoma

The cumulative incidence of histologically confirmed adenomas by age 45 years was 3.6% (95% confidence interval [CI] = 2.2% to 5.6%) for survivors who had radiotherapy to the colorectal area (including TBI), 2.0% (95% CI = 1.3% to 2.8%) for those without such treatments, and 1.0% (95% CI = 0.3% to 2.6%) for siblings (Figure 1). Among survivors with radiotherapy to the colorectal area, the cumulative incidence of adenomas by age 45 years was statistically significantly higher than among siblings (P = .03), and higher than among survivors without radiotherapy to the colorectal area, though this difference was not statistically significant (P = .07).



No. at risk

Survivors with abdominopelvic RT/TBI	4	200	441	690	737	628	469	317	165
Survivors without abdominopelvic RT/TBI	13	1,751	2,987	3,742	3,419	2,719	1,863	1,106	573
Siblings	387	536	637	659	584	490	357	225	129

FIGURE 1. Cumulative incidence of colorectal adenomas for survivors with and without abdominopelvic radiotherapy and for siblings. Pepe-Mori tests were calculated to evaluate differences in cumulative incidences between groups. p = 0.03 for difference between survivors with abdominopelvic RT/TBI vs. siblings, p = 0.07 for difference between survivors with abdominopelvic RT/TBI vs survivors without abdominopelvic RT/TBI, p = 0.29 for difference between survivors without abdominopelvic RT/TBI vs. siblings. The cumulative incidence figure represents univariable comparisons. In multivariable Cox regression analyses in survivors, both abdominopelvic RT (HR=2.1; 95% CI: 1.2-3.6) and TBI (HR=10.6; 95% CI: 5.2-21.4) were statistically significant risk factors. Abbreviations: RT, radiotherapy; TBI, total body irradiation.

Multivariable Cox Regression Analyses Colorectal Adenoma

We then performed multivariable Cox regression analyses to evaluate the role of concomitant characteristics and exposures (Table 3). A history of TBI (hazard ratio [HR]= 10.55, 95% CI = 5.20 to 21.42) or any hematopoietic cell transplantation (HCT; HR = 6.32, 95% CI = 3.19 to 12.55) strongly increased adenoma risk; HCT without TBI did not (HR = 0.87, 95% CI = 0.11 to 7.25, n = 1 case). In addition, survivors who had received abdominopelvic radiotherapy (not including TBI) had a statistically significantly higher risk compared with those without such treatments (HR = 2.12, 95% CI = 1.24 to 3.60) without clear trends of risk according to abdominopelvic radiation dose or estimated exposed colorectal volume (Supplementary Tables 3 and 4). Cisplatin was statistically significantly associated with increased adenoma

risk (HR = 2.81, 95% CI = 1.32 to 5.99; not shown), without strong evidence of a dose response (HR = 2.13, 95% CI = 0.74 to 6.07 for <480 mg/m²; HR=3.85, 95% CI = 1.45 to 10.26 for ≥480 mg/m²; P_{trend} = .62) (Table 3). Cisplatin-associated adenoma risk was slightly attenuated in sensitivity analyses excluding hepatoblastoma survivors (HR = 2.34, 95% CI = 0.98 to 5.56) and excluding 2484 survivors of Li-Fraumeni syndrome (LFS)—associated childhood cancers (leukemia, central nervous system tumors, sarcoma, except Ewing; HR = 2.29, 95% CI = 0.71 to 7.38; not shown). Among all survivors, procarbazine was not associated with adenoma risk (HR = 1.27, 95% CI = 0.50 to 3.19 for <6603 mg/m²; HR = 1.67, 95% CI = 0.66 to 4.23 for ≥6603 mg/m²; P_{trend}=0.79). Procarbazine was statistically significantly associated with adenoma risk among survivors who did not have abdominopelvic radiotherapy/TBI (HR = 2.71, 95% CI = 1.28 to 5.74; not shown). Hepatoblastoma survivors (HR = 27.12, 95% CI = 8.80 to 83.58) and cohort members with a family history of early-onset CRC (n = 15, including five adenoma cases) had strongly increased risks of adenomas (HR = 20.46, 95% CI = 8.10 to 51.70) (Table 3). Adjustments for hepatoblastoma and CRC family history did not materially alter treatment-related risks. To enable comparisons with other studies, we here also report hazard ratios for variables of interest not selected for the final multivariable model shown in Table 3 (see Supplementary Methods), including female sex (HR = 1.04, 95% CI = 0.65 to1.66), medulloblastoma (FAP indicator; HR = 0.39, 95% CI = 0.09 to1.76), carboplatin (HR = 1.09, 95% CI = 0.24 to 5.03), etoposide (HR = 1.20, 95% CI = 0.53 to 2.71), teniposide (HR = 1.92, 95% CI = 0.87 to 4.24), mercaptopurine (HR = 0.69, 95% CI = 0.37 to 1.32; data not shown).

TABLE 3. Multivariable Cox regression analyses for risk of colorectal adenomas*

	Total No.	No. of cases	HR	95% CI	P_{trend}†
Abdominopelvic radiotherapy (excluding total body irradiation)					
No	4,999	57	1.0 (Ref)		
Yes‡	803	20	2.1	1.2-3.6	
Total body irradiation					
No	5,590	67	1.0 (Ref)		
Yes	210	10	10.6	5.2-21.4	
Cisplatin dose, mg/m²§					
No cisplatin	5,371	67	1.0 (Ref)		
<480	269	4	2.1	0.7-6.1	
≥480	164	5	3.9	1.4-10.3	0.62
Procarbazine dose, mg/m²§					
No procarbazine	5,397	66	1.0 (Ref)		
<6,603	288	5	1.3	0.5-3.2	
≥6,603	119	5	1.7	0.7-4.2	0.79

TABLE 3 (CONTINUED).

	Total No.	No. of cases	HR	95% CI	P_{trend} †
Childhood cancer diagnosis of hepatoblastoma					
No	5,800	74	1.0 (Ref)		
Yes	43	4	27.1	8.8-83.6	
Family history of early-onset CRC‖					
No/unknown	5,816	73	1.0 (Ref)		
Yes	15	5	20.5	8.1-51.7	

Abbreviations: CI, confidence interval; Gy, Gray; HR, hazard Ratio.

* Model includes only 76 colorectal adenoma cases due to missing values. Supplementary Table 3 shows univariate results of all variables that were evaluated. Variables that were evaluated in multivariable analysis, but were not statistically significantly associated with adenoma risk and thus not included in this table were: volume of colorectal area in radiation field, maximum prescribed dose to the colorectal area (and interaction between volume and prescribed dose) (see Supplementary Table 4 for more details), carboplatin, childhood cancer diagnosis of medulloblastoma, etoposide, teniposide, mercaptopurin, and hematopoietic cell transplantation. Although hematopoietic cell transplantation was statistically significantly associated with adenoma risk in univariate analysis, this variable did not statistically significantly increase adenoma risk in multivariable analysis when total body irradiation was also in the model. As total body irradiation was still statistically significantly elevated when both variables were in the model, we chose to include total body irradiation in the final model rather than hematopoietic cell transplantation. An indicator variable for a childhood cancer diagnosis of hepatoblastoma was included because hepatoblastoma survivors have a highly increased risk of familial adenomatous polyposis (FAP). All four hepatoblastoma cases had a confirmed genetic diagnosis of FAP.

† Test for trend in continuous dose variable among exposed survivors.

‡ Includes seven survivors (two CRA cases) who received both abdominopelvic radiotherapy (all seven had spinal radiotherapy) and total body irradiation.

§ Categories based on median dose among exposed adenoma cases.

‖ Defined as having a first-degree relative affected by colorectal cancer before age 50 years.

Indications for Colonoscopy

We obtained medical information regarding diagnostic testing preceding colorectal adenoma diagnosis for 42 of 78 cases (Supplementary Table 5). Seventeen adenoma patients had a colonoscopy ordered for abdominal symptoms indicative of colorectal tumors. For another 17 individuals, the adenoma was discovered during medical surveillance in high-risk groups. In eight patients, adenoma represented an accidental finding on imaging/colonoscopy ordered for reasons other than a suspected colorectal tumor. The findings were essentially similar for patients with and without a history of colorectal RT exposure. Results of treatment-related risk factors in multivariable Cox models did not materially change when excluding 17 individuals who received surveillance colonoscopies (not shown).

Colorectal Cancer

Thirteen cohort members had a subsequent primary CRC (SIR = 3.3, 95% CI = 1.8 to 5.7, EAR=1.1/10 000 PY), including eight colon cancers (SIR = 3.9, 95% CI = 1.7 to 7.7, EAR

= 0.8/10 000 PY) and five rectal cancers (SIR = 3.6, 95% CI = 1.2 to 8.5, EAR = 0.5/10 000 PY) (Table 4). Median age at CRC diagnosis was 36.5 years (range = 23.1-56.0). The cumulative incidence of CRC by age 45 years was 0.47% among survivors, compared with 0.15% expected (Supplementary Figure 3). Four CRC patients (30.7%) had received abdominopelvic radiotherapy, five (38.5%) had received other radiotherapy (including one with spinal radiotherapy), and most had some form of prior chemotherapy (n = 11, 84.6%). Four of 13 (30.8%) CRC cases had received alkylating agents; none had received platinum agents. Moreover, nine of 13 patients (69.2%) with subsequent CRC also developed an adenoma; seven of them had a synchronous diagnosis of first adenoma and CRC.

DISCUSSION

Our data show that childhood cancer survivors treated with radiotherapy to the colorectal area —including TBI — are at increased risk of adenomas compared with a sibling comparison group and that childhood cancer survivors are at a more than threefold increased risk of CRC compared with the general population. To our knowledge, this is the first study to assess the risk of and risk factors for histologically confirmed colorectal adenomas among childhood cancer survivors, based on a cohort not subject to systematic colorectal tumor screening with near-complete treatment characterization and follow-up up to January 2017. Moreover, adenoma risk factors include prior treatment with the chemotherapeutic agents cisplatin and procarbazine, a personal history of hepatoblastoma (FAP related), and a family history of early-onset CRC.

We showed an increased risk of CRC in our study group compared with the general population. Over the past decade, several high-quality follow-up studies among very long-term childhood[1,2,19] and adult[4,20-22] cancer survivors reported elevated CRC risk consistent with our results, in particular among survivors of Wilms' tumor and Hodgkin lymphoma after high-dose abdominal radiotherapy.[2,4,19] As most CRCs are preceded by adenomas in the general population,[9] we hypothesized that risk factors for CRC and adenoma are similar. Conversely, Brenner and colleagues estimated from a CRC screening study among older citizens that less than half of all adenomas advance to CRC during a life-time, including decreasing conversion rates with attained age.[23]

TABLE 4. Clinical and histopathological characteristics of patients with a subsequent colorectal cancer

ID	Sex	CC type	Site CRC	Age CC	Year CC	RT treatment CC, Gy, location	CT treatment CC	Age CRC, y	Year CRC	Latency CC-CRC,y	Histology first adenoma	Latency adenoma-CRC	Survival
Included in analysis cohort													
1	F	ALL	Rectum	1	1982	42.5, brain; 18, total spine	As MTX MP V	33	2014	31	Tubular	Synchronous	Alive
2	M	ALL	Sigmoid	3	1982	25, brain	As MTX MP V	22	2002	19	No adenoma	NA	Alive
3	M	ALL	Sigmoid	5	1993	No RT	CY CYC D Et MTX V	27	2015	22	No adenoma	NA	Alive
4	F	HL	Rectum	5	1995	No RT	B Dc E MC V Vb P	35	2015	20	Tubulovillous	Synchronous	Alive
5	F	NHL	Transverse colon	6	1979	25, brain	A CY MC MP P V	31	2004	25	Tubulovillous	Synchronous diagnosis	Alive
6	M	MB	Rectum	5	1973	39, brain; 30, total spine	No CT	41	2009	36	Tubulovillous	Adenoma 2 months before CRC	Deceased
7	F	WT	Colon, NOS	1	1975	20, abdomen	A V	36	2010	34	No adenoma	NA	Deceased
8	F	WT	Ascending colon	2	1974	30, abdomen	A V	40	2012	38	Tubulovillous	Synchronous	Alive
9	M	WT	Rectum	3	1979	29, abdomen	A V	37	2014	34	Tubular	Synchronous	Alive
10	F	WT	Rectum	9	1975	30, abdomen	A V	35	2001	26	Tubular and tubulovillous	Adenoma 4 years after CRC	Alive
11	M	OS	Sigmoid	14	1971	No RT	No CT	55	2013	41	No adenoma	NA	Alive
12	M	RMS	Sigmoid	2	1975	No RT	A CYC D I V	39	2013	37	Tubular	Synchronous	Alive
13	M	RMS	Sigmoid	6	1968	40, neck; 30, head	A MTX	51	2013	45	Tubulovillous	Synchronous	Alive
Excluded from analysis cohort													
14	M	NHL	Caecum	8	1971	40, abdomen	MC P V	36	1998	27	No adenoma	NA	Alive

Abbreviations: A, actinomycine; ALL, acute lymphoblastic leukemia; As, asparginase; B, bleomycin; CC, childhood cancer; CRC, colorectal carcinoma; CT, chemotherapy; CY, cytarabine; CYC, cyclophosphamide; D, doxorubicin; Dc, dacarbazine; E, epirubicin; Et, etoposide; HL, Hodgkin's lymphoma; I, ifosfamide; MB, medulloblastoma; MC, mechlorethamine; MP, 6-mercaptopurine; MTX, methotrexaat; NA, not applicable; NHL, non-Hodgkin's lymphoma; NOS, not otherwise specified; OS, osteosarcoma; P, procarbazine; RMS, rhabdomyosarcoma; RT, radiotherapy; V, vincristine; Vb, vinblastine; WT, Wilms' tumor.

* Excluded, because patient was residing abroad at the time of colorectal carcinoma occurrence and therefore not at risk according to our criteria.

We found that survivors with previous abdominopelvic radiotherapy/TBI were at increased risk of adenomas compared with survivors treated otherwise, and in comparison with siblings. The lack of radiation dose-response is consistent with findings from the only other large study on ionizing radiation and adenoma risk, among Atomic Bomb survivors, who were exposed to much lower median radiation doses.[24] Several factors may contribute to the lack of radiation dose response for adenoma in this exploratory study: the rather limited range of cumulative maximum prescribed dose to the colorectal region (median = 30.0 Gy, interquartile range = 20.0—35.2), the fact that we used surrogates for true absorbed colon/rectum dose, and the limited number of adenoma cases with any radiotherapy exposure to the abdomen. The lack of volume effects may be related to the validity of our proxy (ie, treatment field-based estimation) for exposed colorectal volume; nonetheless, this carefully constructed variable, in combination with treatment dose, provides a more detailed classification of colorectal radiation exposure than used in most other large-scale cohort studies of second tumor risk.

In our cohort, six survivors had more than 10 adenomas, including two cases after abdominopelvic radiotherapy/TBI. All TBI patients underwent HCT, and we hypothesize that HCT-related factors other than ionizing radiation exposure might contribute to the high excess risk, such as immune dysregulation or closer medical follow-up among HCT survivors, who are at substantial risk for chronic health problems.[25,26] Most patients with TBI have received an allogeneic HCT including intense treatment regimens. Despite rigorous adjustment for single agents, some residual confounding may persist.

Previous cisplatin treatment, a putative risk factor for gastrointestinal tract cancer,[1] is associated with adenoma risk in our study. Although cisplatin was often part of hepatoblastoma and bone sarcoma treatment, our sensitivity analyses excluding hepatoblastoma and LFS-associated childhood cancer types suggested that only a small part of the cisplatin-associated risk could be attributed to LFS-associated genetic susceptibility. We also observed a statistically significantly increased risk of adenomas for the alkylating agent procarbazine, but only among survivors without prior abdominopelvic radiotherapy or TBI. Previous childhood cancer survivor studies implicated alkylating agent exposure as a risk factor for CRC[2] and procarbazine as a risk factor for any gastrointestinal tract cancer (53% CRC).[1] Associations with procarbazine have been reported among survivors of young adult cancer.[27-29]

In our study, four (8%) of a total of 52 hepatoblastoma survivors developed an adenoma, all four with a confirmed FAP diagnosis and including three with multiple adenomas. This constellation of tumors constitutes well-established FAP features.[17,30,31] It is conceivable that other cohort members with adenoma have genetic syndromes associated with increased colon tumor risk, such as LFS;[32] based on available data this was not apparent.

A major strength of our study is the large cohort size with joint availability of detailed

individual treatment information and objective data on histologically confirmed adenomas from linkage to the nationwide registry of histo- and cytopathology (PALGA) for more than 95% of the study population.[14] Furthermore, the sibling comparison group enables assessment of global excess risk.

Limitations include the slight chance of false-positive findings with the PALGA linkage on family name, sex, and birth date due to administrative twins. Also, as PALGA attained nation-wide coverage in 1990, we left-truncated the follow-up on January 1, 1990. Only 9% of potential person-years prior to 1990 were missed, predominantly among young individuals (age <30 years) (Supplementary Figure 1). Second, for adenoma cases, we sought information on colonoscopies. This was not attempted for more than 5700 survivors without an adenoma. Although some detection bias may exist, the extent is likely small: Evidence-based DCOG-LATER follow-up recommendations, with adherence in all seven follow-up clinics, do not include active colorectal tumor surveillance, eliminating screening bias. Moreover, less than 2% of cohort members are eligible yet for the population-based CRC screening program for people age 55 to 75 years, which is being implemented during 2014—2019.[33] Therefore, the lack of systematic colorectal tumor surveillance implies that not all incident, asymptomatic adenomas will be known. On the other hand, survivors treated with abdominopelvic radiotherapy and/or TBI are under more frequent late effects clinic surveillance and may experience more abdominal complaints than those treated with chemotherapy only, and may receive more abdominal ultrasounds. This diagnostics tool is not suitable to detect colorectal tumors whereas colonoscopies are mainly used in case of symptoms indicative of tumors or inflammatory conditions. Accordingly, few adenomas (8/42=19%) were discovered incidentally on imaging or during medical follow-up for symptoms other than a suspected colorectal tumor, without clear differences between those with and without abdominopelvic radiotherapy/TBI; a major bias is thus quite unlikely (Supplementary Table 5). Finally a note of caution is in place with regard to the findings for specific chemotherapy agents. It is well-recognized that treatments are not homogeneously distributed in mixed childhood cancer survivorship cohorts.[13,34] As we did not demonstrate clear dose-response trends, we cannot exclude the possibility that some of these agents in fact are surrogates for other factors not captured otherwise.

Further studies are needed to validate our findings; however, this is challenging in most settings as they require joint access to individual treatment data and objective sources for assessment of benign tumors in large cohorts (or nested studies therein). As a majority of our cohort has not yet reached the ages at which incidence of colorectal tumors in the general population is high, continued observational studies of colorectal tumors in childhood cancer survivors are warranted.

Finally, detection of early-stage colorectal tumors decreases CRC-specific mortality.[6] Survivors with a family history of early-onset CRC, a group for whom CRC surveillance was

implemented,[35] were at greater than 20-fold increased risk of developing an adenoma. In our study, almost 70% of the CRC-patients also had an adenoma, often detected around the CRC diagnosis date, which is suggestive of an adenoma-carcinoma sequence in CRC pathogenesis; this hypothesis needs confirmation. Screening among asymptomatic high-risk survivors is being considered.[1-3] At present, the US Children's Oncology Group is the only guideline group recommending a colonoscopy at a minimum of every five years for survivors who received 30 or more Gy abdominopelvic or spinal radiotherapy, from 10 years after radiation or starting at age 35 years, whichever occurs last.[36] National guideline groups have gathered in the International Guideline Harmonization Group (IGHG) to evaluate and harmonize recommendations for surveillance of late effects after treatment for childhood and young adult cancer based on evidence-based methods.[37-39] IGHG's work on CRC surveillance is scheduled to start shortly.

In conclusion, we provide new evidence for excess risk of histologically confirmed colorectal adenomas among childhood cancer survivors. Treatment-related risk factors for adenoma were abdominopelvic radiotherapy, TBI/HCT, cisplatin, and procarbazine. Adenoma risk was strongly increased in hepatoblastoma survivors (FAP related) and in survivors with a family history of early-onset CRC, as expected. A full benefit-vs-harm evaluation of CRC screening among high-risk cancer survivors is warranted.

Acknowledgements

The DCOG-LATER Study Group for colorectal adenomas and cancers includes the following persons: B.M.P. Aleman (The Netherlands Cancer Institute, Amsterdam); M.H. van den Berg (VU University Medical Center, Amsterdam); D. Bresters (Willem-Alexander Children's Hospital/Leiden University Medical Center, Leiden); H.N. Caron (Emma Children's Hospital/Academic Medical Center, Amsterdam); L.A. Daniels (Leiden University Medical Center); W. Dolsma (University of Groningen/University Medical Center Groningen); E. van Dulmen-den Broeder (VU University Medical Center, Amsterdam); M.A. Grootenhuis (Emma Children's Hospital/Academic Medical Center, Amsterdam, and Princess Máxima Center for Pediatric Oncology, Utrecht); C.J. Haasbeek (VU University Medical Center, Amsterdam); J.G. den Hartogh (Dutch Childhood Cancer Parent Organisation (VOKK), Nieuwegein); M. Hauptmann (The Netherlands Cancer Institute, Amsterdam); M. van der Heiden-van der Loo (Dutch Childhood Oncology Group, The Hague); M.M. van den Heuvel-Eibrink (Sophia Children's Hospital/Erasmus Medical Center, Rotterdam and Princess Máxima Center for Pediatric Oncology, Utrecht); N. Hollema (Dutch Childhood Oncology Group, The Hague); G.O. Janssens (University Medical Center Utrecht, Utrecht and Princess Máxima Center for Pediatric Oncology, Utrecht); M.C. Jongmans (Radboud University Medical Center, Nijmegen, University Medical Center Utrecht, Utrecht, and Princess Máxima Center for Pediatric Oncology, Utrecht); M.W.M. Jaspers (Academic Medical Center, Amsterdam);

J.L. Kok (Emma Children's Hospital/Academic Medical Center, Amsterdam); L.C.M. Kremer (Emma Children's Hospital/Academic Medical Center, Amsterdam); F.E. van Leeuwen (The Netherlands Cancer Institute, Amsterdam); J. Loonen (Radboud University Medical Center, Nijmegen); J.H. Maduro (University of Groningen/University Medical Center Groningen); S.J.C.M.M. Neggers (Erasmus Medical Center, Rotterdam); F. Oldenburger (Academic Medical Center, Amsterdam); L.I. Overbeek (PALGA Foundation, Utrecht); H.J. van der Pal (Princess Máxima Center for Pediatric Oncology, Utrecht); A. Postma (Dutch Childhood Oncology Group, The Hague); J.G. de Ridder-Sluiter (Princess Máxima Center for Pediatric Oncology, Utrecht); C.M. van Rij (Erasmus Medical Center, Rotterdam); C.M. Ronckers (Emma Children's Hospital/Academic Medical Center, Amsterdam); J.C. Teepen (Emma Children's Hospital/Academic Medical Center, Amsterdam); R.J. Tersteeg (University Medical Center Utrecht, Utrecht); W.J.E. Tissing (Beatrix Children's Hospital/University of Groningen/University Medical Center Groningen, Groningen); A.B. Versluys (Wilhelmina Children's Hospital/University Medical Center Utrecht, Utrecht); M.J. van de Vijver (Academic Medical Center, Amsterdam); J Zsíros (Emma Children's Hospital/Academic Medical Center, Amsterdam).

The funders had no role in design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

We thank all data managers in the seven participating centers and Aslihan Mantici and Anja van Eggermond for obtaining the data for this study. Furthermore, we thank the following other members of the DCOG-LATER group for their contributions: Lilian Batenburg, Margreet Veening, Marloes Louwerens, Gea Huizinga, Lideke van der Steeg, and Andrica de Vries. We thank the staff of the PALGA Foundation for providing record linkage data on colorectal tumors from their registry. We also thank the Netherlands Cancer Registry and Michael Schaapveld for providing population reference rates for colorectal cancer.

REFERENCES

1. Henderson TO, Oeffinger KC, Whitton J et al. Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study. Ann Intern Med 2012; 156: 757-766, W-260.
2. Nottage K, McFarlane J, Krasin MJ et al. Secondary colorectal carcinoma after childhood cancer. J Clin Oncol 2012; 30: 2552-2558.
3. Reulen RC, Frobisher C, Winter DL et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA 2011; 305: 2311-2319.
4. van Eggermond AM, Schaapveld M, Janus CP et al. Infradiaphragmatic irradiation and high procarbazine doses increase colorectal cancer risk in Hodgkin lymphoma survivors. Br J Cancer 2017; 117: 306-314.
5. von Karsa L, Patnick J, Segnan N et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy 2013; 45: 51-59.
6. Lin JS, Piper MA, Perdue LA et al. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2016; 315: 2576-2594.
7. Levin B, Lieberman DA, McFarland B et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008; 134: 1570-1595.
8. Daly PE, Samiee S, Cino M et al. High prevalence of adenomatous colorectal polyps in young cancer survivors treated with abdominal radiation therapy: results of a prospective trial. Gut 2016.
9. Leslie A, Carey FA, Pratt NR, Steele RJ. The colorectal adenoma-carcinoma sequence. Br J Surg 2002; 89: 845-860.
10. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. Cancer 1975; 36: 2251-2270.
11. Winawer SJ, Zauber AG, Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329: 1977-1981.
12. Zauber AG, Winawer SJ, O'Brien MJ et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012; 366: 687-696.
13. Teepen JC, van Leeuwen FE, Tissing WJ et al. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: role of chemotherapy. J Clin Oncol 2017; 35: 2288-2298.
14. Casparie M, Tiebosch AT, Burger G et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007; 29: 19-24.
15. Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? Stat Med 1993; 12: 737-751.
16. Yasui Y, Liu Y, Neglia JP et al. A methodological issue in the analysis of second-primary cancer incidence in long-term survivors of childhood cancers. Am J Epidemiol 2003; 158: 1108-1113.

17. Hughes LJ, Michels VV. Risk of hepatoblastoma in familial adenomatous polyposis. Am J Med Genet 1992; 43: 1023-1025.
18. Forman D, Bray F, Brewster DH et al. Cancer incidence in five continents. Vol. X. IARC Scientific Publications No. 164. Lyon: International Agency for Research On Cancer. 2014.
19. Tukenova M, Diallo I, Anderson H et al. Second malignant neoplasms in digestive organs after childhood cancer: a cohort-nested case-control study. Int J Radiat Oncol Biol Phys 2012; 82: e383-390.
20. Hodgson DC, Gilbert ES, Dores GM et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. J Clin Oncol 2007; 25: 1489-1497.
21. Schaapveld M, Aleman BM, van Eggermond AM et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med 2015; 373: 2499-2511.
22. Travis LB, Fossa SD, Schonfeld SJ et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 2005; 97: 1354-1365.
23. Brenner H, Altenhofen L, Stock C, Hoffmeister M. Natural history of colorectal adenomas: birth cohort analysis among 3.6 million participants of screening colonoscopy. Cancer Epidemiol Biomarkers Prev 2013; 22: 1043-1051.
24. Ron E, Wong FL, Mabuchi K. Incidence of benign gastrointestinal tumors among atomic bomb survivors. Am J Epidemiol 1995; 142: 68-75.
25. Chow EJ, Anderson L, Baker KS et al. Late effects surveillance recommendations among survivors of childhood hematopoietic cell transplantation: A Children's Oncology Group Report. Biol Blood Marrow Transplant 2016; 22: 782-795.
26. Morton LM, Saber W, Baker KS et al. National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Subsequent Neoplasms Working Group Report. Biol Blood Marrow Transplant 2017; 23: 367-378.
27. Morton LM, Dores GM, Curtis RE et al. Stomach cancer risk after treatment for hodgkin lymphoma. J Clin Oncol 2013; 31: 3369-3377.
28. van den Belt-Dusebout AW, Aleman BM, Besseling G et al. Roles of radiation dose and chemotherapy in the etiology of stomach cancer as a second malignancy. Int J Radiat Oncol Biol Phys 2009; 75: 1420-1429.
29. Dores GM, Curtis RE, van Leeuwen FE et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. Ann Oncol 2014; 25: 2073-2079.
30. Giardiello FM, Offerhaus GJ, Krush AJ et al. Risk of hepatoblastoma in familial adenomatous polyposis. J Pediatr 1991; 119: 766-768.
31. Lindor NM, McMaster ML, Lindor CJ et al. Concise handbook of familial cancer susceptibility syndromes - second edition. J Natl Cancer Inst Monogr 2008; 1-93.
32. Yurgelun MB, Masciari S, Joshi VA et al. Germline TP53 mutations in patients with early-onset colorectal cancer in the Colon Cancer Family Registry. JAMA Oncol 2015; 1: 214-221.
33. Schippers E. Besluit invoering bevolkingsonderzoek naar darmkanker [Decision to implement population screening for coloretcal cancer]. 2011 http://www.rivm.nl/Documenten_en_publi caties/Algemeen_Actueel/Uitgaven/Preventie_Ziekte_Zorg/Darmkankerscreening/Brief_besluit_minister_VWS_1_juni_2011. Accessed

May 10, 2017.

34. Ronckers CM, Sigurdson AJ, Stovall M et al. Thyroid cancer in childhood cancer survivors: a detailed evaluation of radiation dose response and its modifiers. Radiat Res 2006; 166: 618-628.
35. Nederlandse Vereniging van Maag-, Darm- en Leverartsen. Nederlandse Richtlijn Coloscopie Surveillance; May 2013. https://www.mdl.nl/sites/www.mdl.nl/files/richlijnen/Richtlijn_Colo scopie_Surveillance_definitief_2013.pdf. Accessed March 16, 2017.
36. Children's Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Version 4.0. Monrovia, CA: Children's Oncology Group; October 2013. http://www.survivorshipguidelines.org. Accessed March 10, 2017.
37. Kremer LC, Mulder RL, Oeffinger KC et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Pediatr Blood Cancer 2013; 60: 543-549.
38. Armenian SH, Hudson MM, Mulder RL et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2015; 16: e123-136.
39. Mulder RL, Kremer LC, Hudson MM et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2013; 14: e621-629.

SUPPLEMENTARY MATERIALS

Supplementary Methods

The following established or putative risk factors for colorectal adenomas/cancer were tested in multivariable Cox proportional hazards models: radiotherapy to the colorectal area, procarbazine platinum agents (cisplatin and carboplatin), family history of CRC, and indicator variables for hepatoblastoma and for medulloblastoma; like colon adenoma these childhood cancer types belong to the spectrum of tumors associated with familial adenomatous polyposis (FAP). Both the volume of the colorectal area exposed to radiation as well as radiation dose to the colorectal area were evaluated. Moreover, we included a dose-response evaluation for procarbazine, based on growing evidence for carcinogenic effects of this alkylating agent, in particular among Hodgkin lymphoma patients who often received mixtures of alkylating agents [1]. Effect modification of radiation dose to the colorectal area by tertiles of colorectal volume exposed to radiation was also evaluated by comparing a model with and without effect modification using a likelihood ratio test. Age at childhood cancer diagnosis, sex, and treatment-related factors (chemotherapy agents other than those selected a priori and hematopoietic cell transplantation) with 5 or more exposed adenoma cases were tested in univariable Cox proportional hazards models. All variables with a p value <0.1 in univariable analyses were tested in multivariable Cox proportional hazards models in addition to the risk factors selected based on prior knowledge. In multivariable models, chemotherapy agents were categorized according to median dose. In the final model we included the following: 1) All variables that remained statistically significantly associated with the outcome of interest in multivariable analyses ($p < 0.05$), or 2) changed the effect of other variables with more than 10%, and 3) the procarbazine dose-response evaluation (to allow for future contributions to systematic reviews/pooled analyses, regardless of the significance level) were included in the final model. Once the final multivariable model was established (i.e., Table 3), we re-entered the other a priori determined treatment variables one-by-one to obtain risk estimates as mentioned in the results section. Tests for linear trend were based on the likelihood ratio for a model with the respective continuous variable, based on exposed subjects only, unless otherwise specified.

Reference Supplementary Methods

1. Teepen JC, de Vroom SL, van Leeuwen FE et al. Risk of subsequent gastrointestinal cancer among childhood cancer survivors: A systematic review. Cancer Treat Rev 2016; 43: 92-103.

SUPPLEMENTARY TABLE 1. Classification estimated volume of colorectal area exposed to radiotherapy

Included fields	Assigned percentage of colorectal area in radiation field	Percentage of colorectal area in radiation field
		1-25 %
Spleen	15%	
Spinal, unknown location	15%	
Pelvis, right	15%	
(Cranio)spinal	20%	
Spinal, lumbal or sacral	20%	
Para-aortic	20%	
Liver	20%	
Pelvis, left	25%	
Pelvis, unknown laterality	25%	
Inverted Y without spleen	25%	
Total node (excluding spleen)	25%	
		26-50%
Pelvis, bilateral	35%	
Para-aortic plus spleen	35%	
Inverted Y plus spleen	40%	
Total node (including spleen)	40%	
		51-75%
Abdomen and pelvis, left	60%	
Abdomen and pelvis, right	60%	
Abdomen and pelvis, unknown laterality	75%	
		76-100%
Abdomen and pelvis, bilateral	100%	
Total body irradiation*	100%	

* Total body irradiation was evaluated separately in the multivariable Cox regression models.

SUPPLEMENTARY TABLE 2. Included PALGA diagnosis codes for excerpts on colorectal tumors*

	COLORECTAL CANCER		COLORECTAL ADENOMA	
Topography	**Code**	**Text**	**Code**	**Text**
	T68	Colon	T68	Colon
	T69	Rectum	T69	Rectum
	T50	Intestine, NOS	T50	Intestine, NOS
Morphology	**Code**	**Text**		
	M8…2; M9…2	Carcinoma in situ	M8…0; M9…0	Benign neoplasm
	M8…3; M9…3	Malignant neoplasm		
	M8…4	Microinvasive neoplasm		
	M8…5	Intramucosal neoplasm		
	M8…6; M9….6	Metastatic neoplasm		
	M8…9	Neoplasm, unknown origin		

Abbreviations: NOS, not otherwise specified.

* Codes are originally derived from SNOMED (Systematized Nomenclature of Medicine), College of American Pathologists, version 1982.

SUPPLEMENTARY TABLE 3. Univariable Cox regression analyses for potential risk factors for colorectal adenomas

	N total	N cases	HR	95% CI
Variables selected based on basis of prior knowledge*				
Abdominopelvic radiotherapy (excluding total body irradiation)				
No	4,999	57	1.0 (Ref)	
Yes†	803	20	1.7	1.0-2.8
Volume of colorectal area in radiation field (excluding total body irradiation) ‡				
1-50%	411	7	1.0 (Ref)	
51-100%	328	10	1.0	0.4-2.4
Maximum prescribed radiation dose to the colorectal area‡				
<30 Gy	365	11	1.0 (Ref)	
30+ Gy	423	9	0.7	0.3-1.7
Procarbazine				
No	5,397	66	1.0 (Ref)	
Yes	407	10	1.3	0.7-2.6
Cisplatin				
No	5,371	67	1.0 (Ref)	
Yes	433	9	3.0	1.5-6.1
Carboplatin				
No	5,396	74	1.0 (Ref)	
Yes	409	2	1.6	0.4-6.8

SUPPLEMENTARY TABLE 3 (CONTINUED).

	N total	N cases	HR	95% CI
Childhood cancer diagnosis of hepatoblastoma				
No	5,800	74	1.0 (Ref)	
Yes	43	4	23.0	8.2-64.4
Childhood cancer diagnosis of medulloblastoma				
No	5,690	76	1.0 (Ref)	
Yes	153	2	1.0	0.2-4.1
Family history of early-onset CRC§				
No/unknown	5,816	73	1.0 (Ref)	
Yes	15	5	21.4	8.6-53.3
Other variables‖				
Sex				
Male	3,269	43	1.0 (Ref)	
Female	2,574	35	1.0	0.6-1.5
Age at childhood cancer diagnosis				
<5 years	2,641	23	1.0 (Ref)	
5-9 years	1,583	21	1.0	0.6-1.9
10+ years	1,619	34	0.8	0.4-1.4
Total body irradiation¶				
No	5,590	67	1.0 (Ref)	
Yes	210	10	7.2	3.6-14.1
Mechlorethamine				
No	5,502	66	1.0 (Ref)	
Yes	302	10	1.6	0.8-3.0
Cyclophosphamide				
No	3,602	47	1.0 (Ref)	
Yes	2,205	29	1.4	0.9-2.2
Doxorubicin				
No	3,923	52	1.0 (Ref)	
Yes	1,881	24	1.4	0.8-2.2
Daunorubicin				
No	4,736	64	1.0 (Ref)	
Yes	1,071	12	1.4	0.7-2.6
Etoposide¶				
No	4,866	65	1.0 (Ref)	
Yes	939	11	3.1	1.6-6.2
Teniposide¶				
No	5,410	68	1.0 (Ref)	
Yes	394	8	2.5	1.2-5.2
Vincristine				
No	1,725	27	1.0 (Ref)	
Yes	4,084	49	1.1	0.7-1.9

SUPPLEMENTARY TABLE 3 (CONTINUED).

	N total	N cases	HR	95% CI
Cytarabine				
No	3,703	56	1.0 (Ref)	
Yes	2,105	20	1.3	0.8-2.2
Methotrexate				
No	3,328	54	1.0 (Ref)	
Yes	2,478	22	0.7	0.4-1.2
Thioguanine				
No	5,074	69	1.0 (Ref)	
Yes	730	7	1.6	0.7-3.5
Mercaptopurine¶				
No	3,936	63	1.0 (Ref)	
Yes	1,872	13	0.6	0.3-1.1
Haematopoietic cell transplantation¶				
No	5,404	65	1.0 (Ref)	
Yes	371	11	5.8	3.0-11.2

Abbreviations: CI, confidence interval; CRC, colorectal cancer; Gy, Gray; HR, hazard ratio; N, number.

* Variables were selected on basis of prior knowledge on risk factors for colorectal adenoma and cancer.

† Includes 7 survivors (2 adenoma cases) who received both abdominopelvic radiotherapy (all 7 had spinal radiotherapy) and total body irradiation.

‡ Because abdominopelvic radiotherapy (excluding total body irradiation) (yes vs. no) was added to a model with this variable, estimates represent effects in exposed cases only. Total body irradiation was not included in volume and prescribed dose calculation. Volume and dose variables represent abdominopelvic radiation only.

§ Defined as having a first-degree relative affected by colorectal cancer before age 50 years.

|| Variables with $p<0.1$ were tested in multivariable analyses and retained if $p<0.05$. Only treatment variables with at least 5 adenoma cases exposed to the variable were assessed.

¶ $p<0.1$. Variable was tested in multivariable analyses and retrained if $p<0.05$.

SUPPLEMENTARY TABLE 4. Multivariable Cox regression analyses for risk of colorectal adenomas with joint effects of radiation volume and dose

	N total	N cases	HR univariable*	95% CI	HR multivariable*†	95% CI
Estimated volume of colorectal area in radiation field/maximum radiation dose to the colorectal area‡						
Volume 1-50% / dose <30 Gy	176	5	1.0 (ref)		1.0 (ref)	
Volume 1-50% / dose ≥30 Gy	289	3	0.4	0.1-1.5	0.3	0.1-1.4
Volume 51-100% / dose <30 Gy	200	6	0.8	0.2-2.7	0.8	0.2-2.8
Volume 51-100% / dose ≥30 Gy	134	6	1.0	0.3-3.3	0.9	0.3-3.1

Abbreviations: CI, confidence interval; Gy, Gray; HR, hazard ratio; N, number; TBI, total body irradiation.

* Patients without abdominopelvic radiotherapy were coded in the same group as those with a volume 1-50% / dose <30 Gy, but because an indicator variable for abdominopelvic radiotherapy was added to the model, risk estimates are for subjects exposed to abdominopelvic radiotherapy only.

† Model includes only 76 colorectal adenoma cases due to missing values. Model was additionally adjusted for TBI (yes vs. no), cisplatin (no, <480 mg/m², ≥480 mg/m²), procarbazine (no, <6,603 mg/m², ≥6,603 mg/m²), hepatoblastoma (yes vs. no), and first-degree relative affected by colorectal cancer before age 50 (yes vs. no).

‡ TBI was not included in volume and prescribed dose calculation. Volume / dose represents abdominopelvic radiation only.

SUPPLEMENTARY TABLE 5. Overview reasons for colonoscopy in detecting colorectal adenomas among survivors*

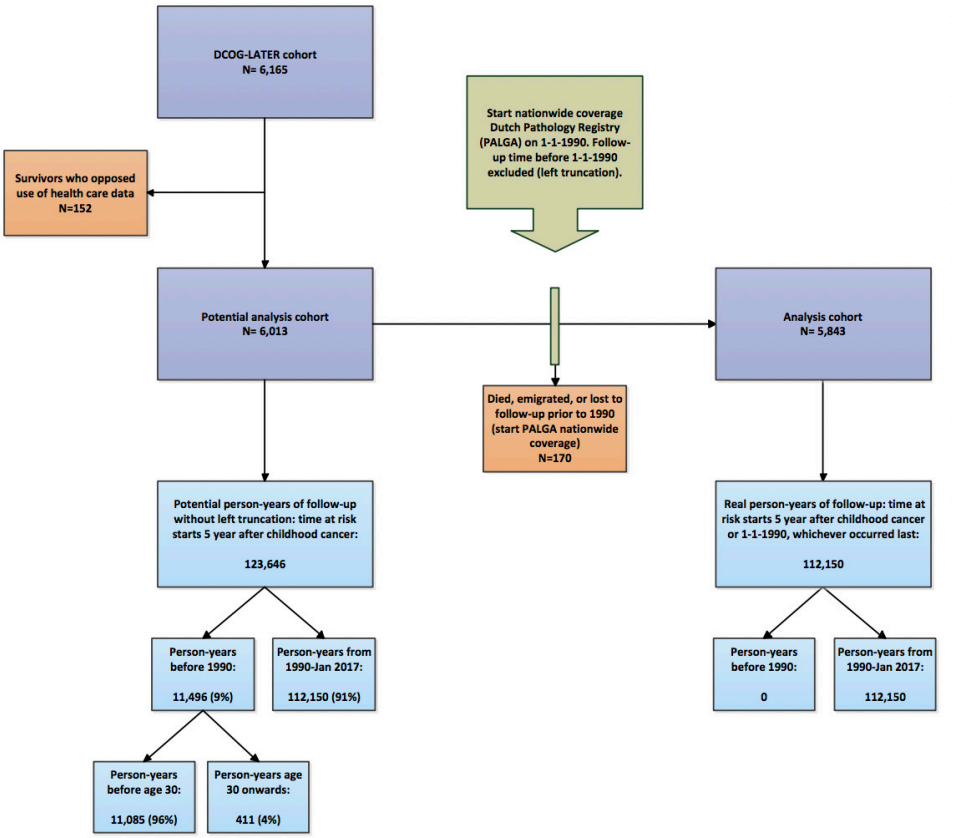
		Abdominopelvic radiotherapy/TBI		No abdominopelvic radiotherapy/TBI†	
Reason colonoscopy category	**Reason colonoscopy detail**	**N**	**%‡**	**N**	**%‡**
Specific colorectal tumor-related symptoms		**10**	**55.6**	**7**	**29.2**
	Anemia	2	11.1	2	8.3
	Rectal blood loss	4	22.2	1	4.2
	Defecation abnormalities	1	5.6	0	0.0
	Gastrointestinal complaints, unknown origin	3	16.7	4	16.7
Screening or surveillance colonoscopy because of (possible) genetic predisposition for colorectal tumors		**4**	**22.2**	**8**	**33.3**
	Diagnosed with familial adenomatous polyposis	1	5.6	5	20.8
	Family member(s) with colorectal tumors having a (possible) genetic predisposition	2	11.1	3	12.5
	Earlier colorectal cancer diagnosis	1	5.6	0	0.0
Screening or surveillance colonoscopy for other reasons		**1**	**5.6**	**4**	**16.7**
	Crohn's disease	0	0.0	1	4.2
	As part of trial to assess the value of colonoscopy in Hodgkin lymphoma patients	1	5.6	1	4.2
	Increased risk of dysplasia due to urine derivation after bladder extirpation	0	0.0	2	8.3
Accidental finding on imaging/colonoscopy reasons other than suspected colorectal tumor		**3**	**16.7**	**5**	**20.8**
	Abnormality in colorectal area on PET scan for other cancer	0	0.0	2	8.3
	Searching for primary tumor location after finding lymph node metastases of adenocarcinoma of unknown origin	1	5.6	0	0.0
	Suspected for Behçet's disease, colonoscopy to rule out inflammatory bowel disease	0	0.0	1	4.2
	Suspected CMV colitis or graft-versus-host disease after hematopoietic cell transplantation	0	0.0	1	4.2
	Diarrhea	1	5.6	1	4.2
	Abnormality on abdominal CT scan performed because of hemochromatosis.	1	5.6	0	0.0
Reason not retrieved		**10**		**25**	

Abbreviations: CMV, cytomegolavirus; CT, computed tomography; PET, positron emission tomography.

* For 1 adenoma case, treatment details were not known and this case is thus not included in the table.

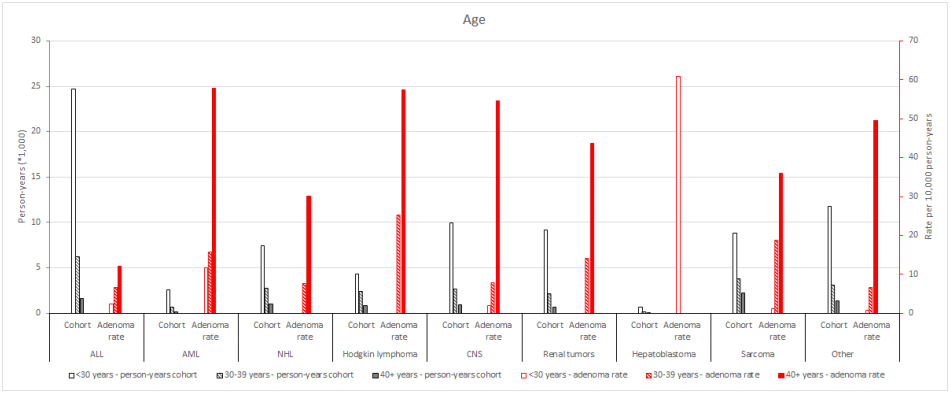
† The group "No abdominopelvic radiotherapy/TBI" only includes survivors and thus not siblings. For siblings, we were not able to retrieve the reason for colonoscopy.

‡ Denominator for calculating percentages were cases with a known reason for colonoscopy only (N=18 for survivors with abdominopelvic radiotherapy/TBI and N=24 for survivors without abdominopelvic radiotherapy/TBI).

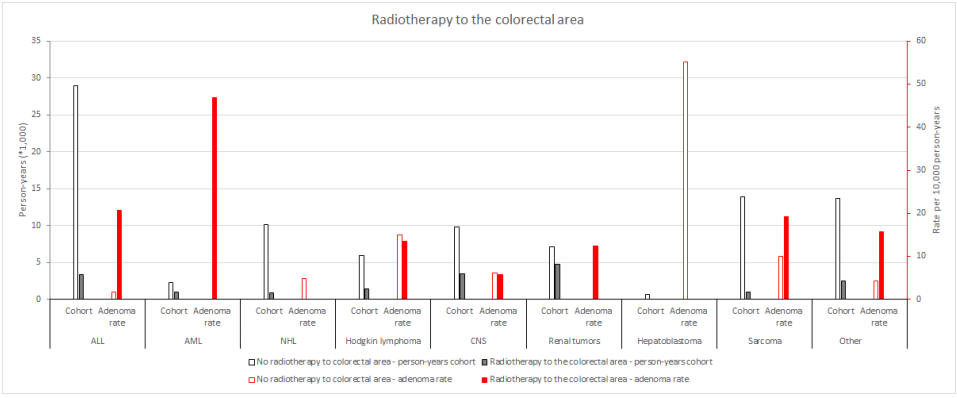


SUPPLEMENTARY FIGURE 1. Flowchart overview inclusion of cohort and follow-up time

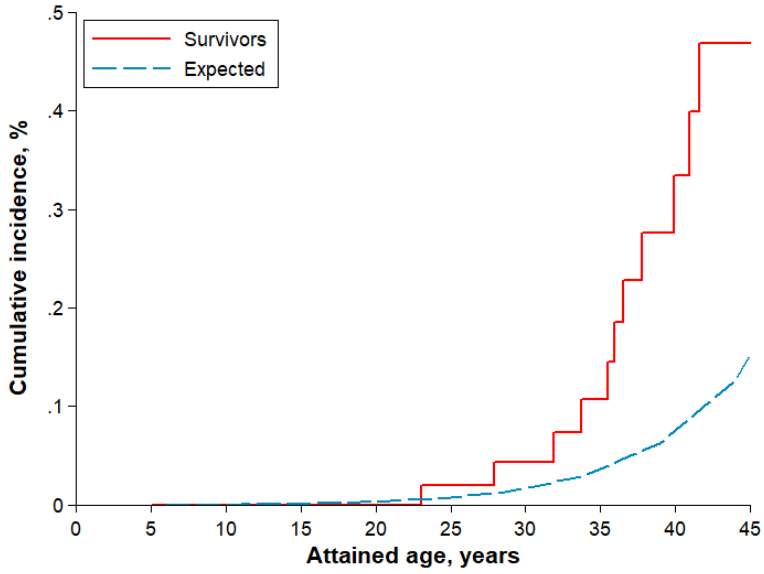
PANEL A - BY AGE



PANEL B – BY RADIOTHERAPY TO THE COLORECTAL AREA STATUS



SUPPLEMENTARY FIGURE 2. Description of heterogeneity of age (panel A) and radiotherapy to the colorectal area status (Panel B) by childhood cancer type. Person-years of follow-up (left axis, grey bars) and rates of colorectal adenomas (right axis, red bars) are shown in the figure. In Panel A, individuals contributed person-years to a specific age category if they had follow-up time during that interval, irrespective of their attained age at end of follow-up.



No. at risk	18	1,960	3,445	4,440	4,184	3,370	2,355	1,437	751

SUPPLEMENTARY FIGURE 3. Cumulative incidence of colorectal cancers in the DCOG-LATER cohort and expected cumulative incidence in the general population